

Drug Regulatory Environment - Brazil

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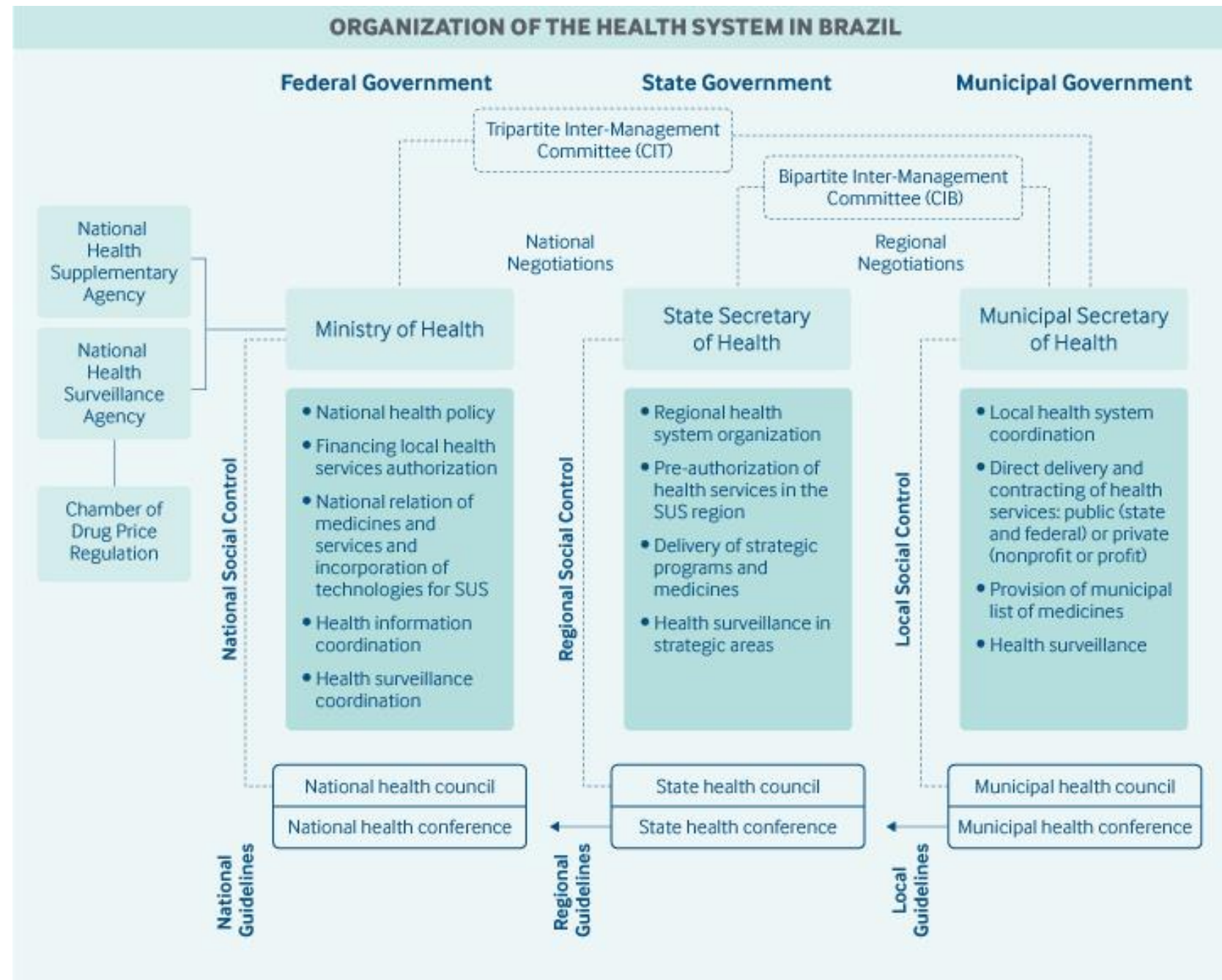
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July/2020

Brazil in Numbers

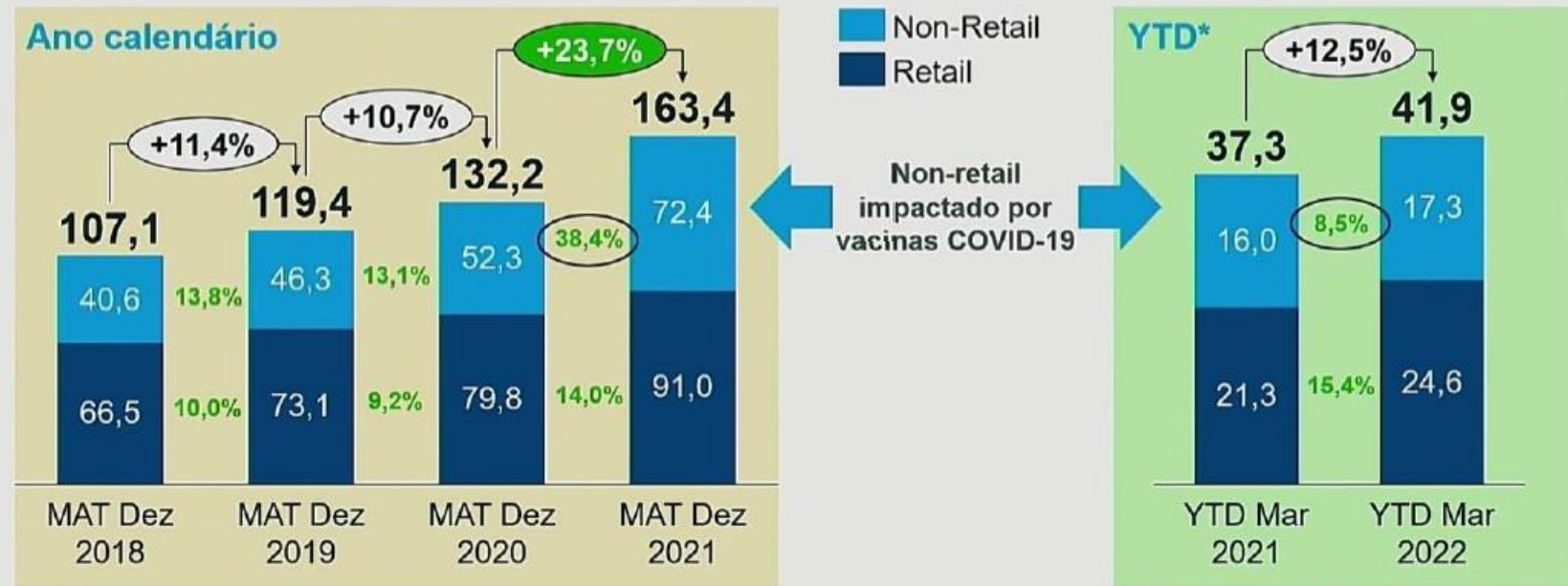
- 5th biggest Country in territory (8.516.000 km²)
- Population estimated in 214.800.000 people
SOURCE: Brazilian Institute of Geography and Statistics
- GDP Nominal: 1,645.84 Billons USD - 12th in world rank
SOURCE: statisticstimes.com
- GDP PPP: 3,437.61 Billons USD - 8th in world rank
SOURCE: statisticstimes.com

Brazilian Healthcare System



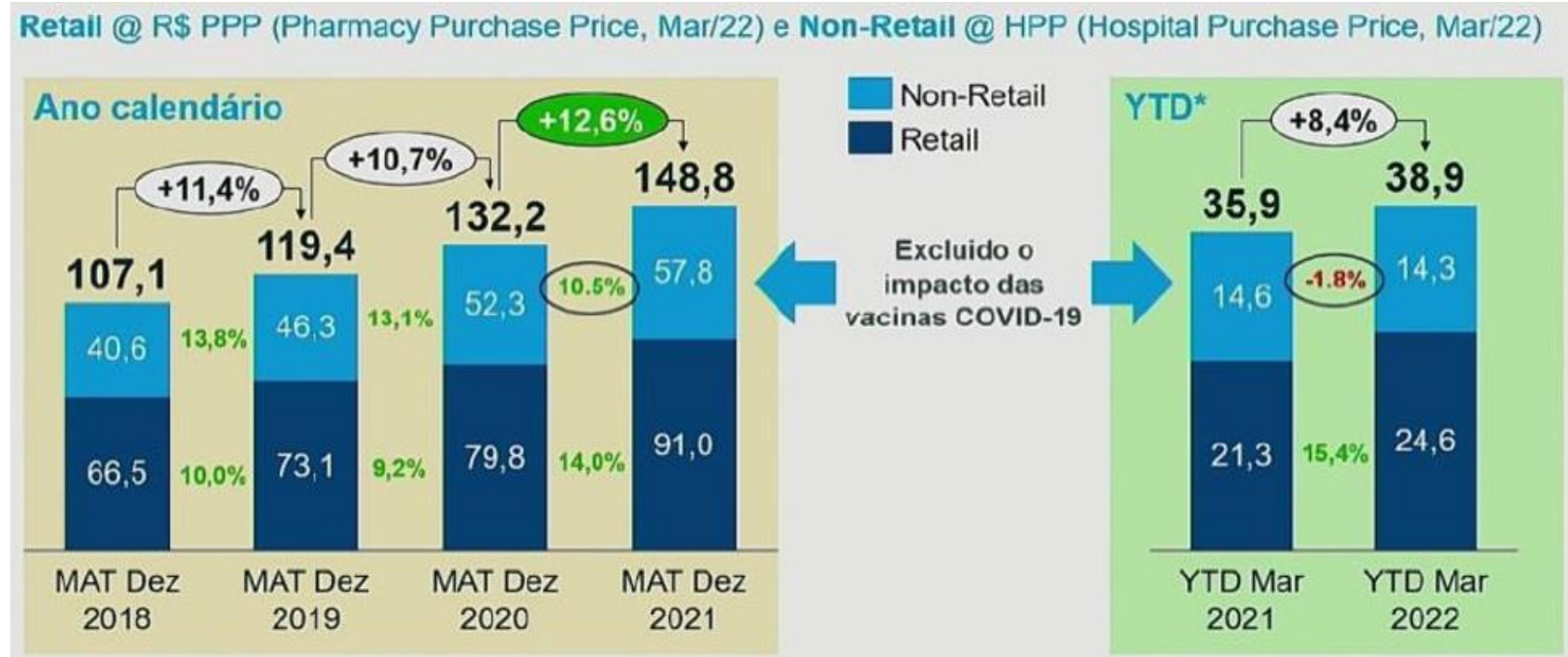
Brazilian Pharma Market - 2021

Retail @ R\$ PPP (Pharmacy Purchase Price, Mar/22) e Non-Retail @ HPP (Hospital Purchase Price, Mar/22)



Source: IQVIA March 2022 (Pharmacy Purchase Price); IQVIA Non-Retail March 2022 (Hospital Purchase Price)

Brazilian Pharma Market – 2021 Without Covid Vaccines Impact



Source: IQVIA March 2022 (Pharmacy Purchase Price); IQVIA Non-Retail March 2022 (Hospital Purchase Price)

Brazilian Pharmaceutical Marketing – Mundial Ranking

2023		
Rk	Country	% of US
1	United States	100
2	China	27
3	Japan	12
4	Germany	10
5	 BRAZIL	7
6	Italy	6
7	 France	6
8	United Kingdom	5
9	 India	5
10	 Spain	4

2018		
Rk	Country	% of US
1	United States	100
2	China	28
3	Japan	18
4	Germany	11
5	France	7
6	Italy	7
7	 BRAZIL	6
8	 United Kingdom	6
9	Spain	5
10	Canada	5

Obs: The exchange rate can also affect the position in the ranking

2013		
Rk	Country	% of US
1	United States	100
2	 China	28
3	 Japan	24
4	 Germany	12
5	 France	10
6	Italy	7
7	 United Kingdom	6
8	 BRAZIL	5
9	 Spain	5
10	 Canada	5

Source: IQVIA, The Global Use of Medicine in 2019 and Outlook 2023, January 2019.

Created in 1999, was one of the first Agencies created in Brazil, untied to the Ministry of Health, with a stable board of directors with fixed mandate.

Regulates: Medicinal Products, Medical Devices, Cosmetics, Tobacco Products, Sanitizing Products, Customs and borders

ICH Member since 2018 as regulatory member, and part of the Management Committee since 2021.

PIC/s Member since 2020, the GMP, after harmonizing the GMP requirements.

Requirements for a New Drug Importer

- MAH must be a Brazilian company
- Drug Product importer must have:
 - Local warehouse that allows to handle products at the final storage conditions
 - QA system with specific SOPs to support the operation
 - QC laboratory able to perform a complete QC analysis, except for:
 - Rare diseases Drugs with transport chain qualified
 - Biological products with transport chain qualified
 - Local Sanitary License (annually renewed)
 - Federal Working Authorization (AFE)
 - Good Warehousing & Distribution Practice adherence
 - Pharmacovigilance capabilities with a Local Qualified Person

Drug Products Categories

Synthetic drug product

- New drug (radical innovation)
- Incremental Innovation (New dosage form, strength, posology, indication)
- Generic/Brand generic (similar drug product)

Biological Drug

- New Drug Pathway
- Individual Development Pathway
- Comparison Development Pathway

Good Manufacturing Practices

- Guidelines harmonized with PIC/s since 2019
- Certification valid for 2 years
- Issued by Manufacturing line
- All involved on the manufacturing chain must be certified
 - API manufacturer (Biological & synthetic)
 - Intermediates
 - Primary & secondary packing sites

Main Requirements

- API registration (CADIFA)
 - Only for synthetic drug substance
 - AH may be the API manufacturer or local company
 - Complete DMF submitted in CTD format (including close part)
 - Accepted dossier in English
 - GMP certification in parallel to the CADIFA request
 - Peculiarities
 - Close part can be sent by the API manufacturer
 - Impurities must be well known and established according to ICH guidance (Q3 guides).
 - Special attention to ICH M7

Main Requirements

- New Drug Application

- Anvisa GMP certification (request mandatory for submission; certificate mandatory for MA approval)
- Complete CTD format (M2, M3, M4 and M5) or Anvisa format (same information, different organization)
- M2 must be presented in Portuguese
- Clinical Trials (Phase I, II and III)
- Peculiarities - M3
 - Stability Studies according to Zone IVB conditions ($30\pm 2^{\circ}\text{C}/70\%\pm 5\%\text{HR}$)
 - Photostability is required, according to ICH guidance
 - QC methods validated according to the local regulation. Local QC methods must be transferred and validated.
 - Degradation profile must be assessed
 - Must present the process validation report

Main Requirements

- Incremental innovation
 - Only for synthetic drug substance
 - Anvisa GMP Certification
 - Complete CTD format (M2, M3, M4 and M5) or Anvisa format (same information, different organization)
 - Accepted dossier in English or Spanish
 - GMP certification required for API and Finished product

Main Requirements

- New Biological Product

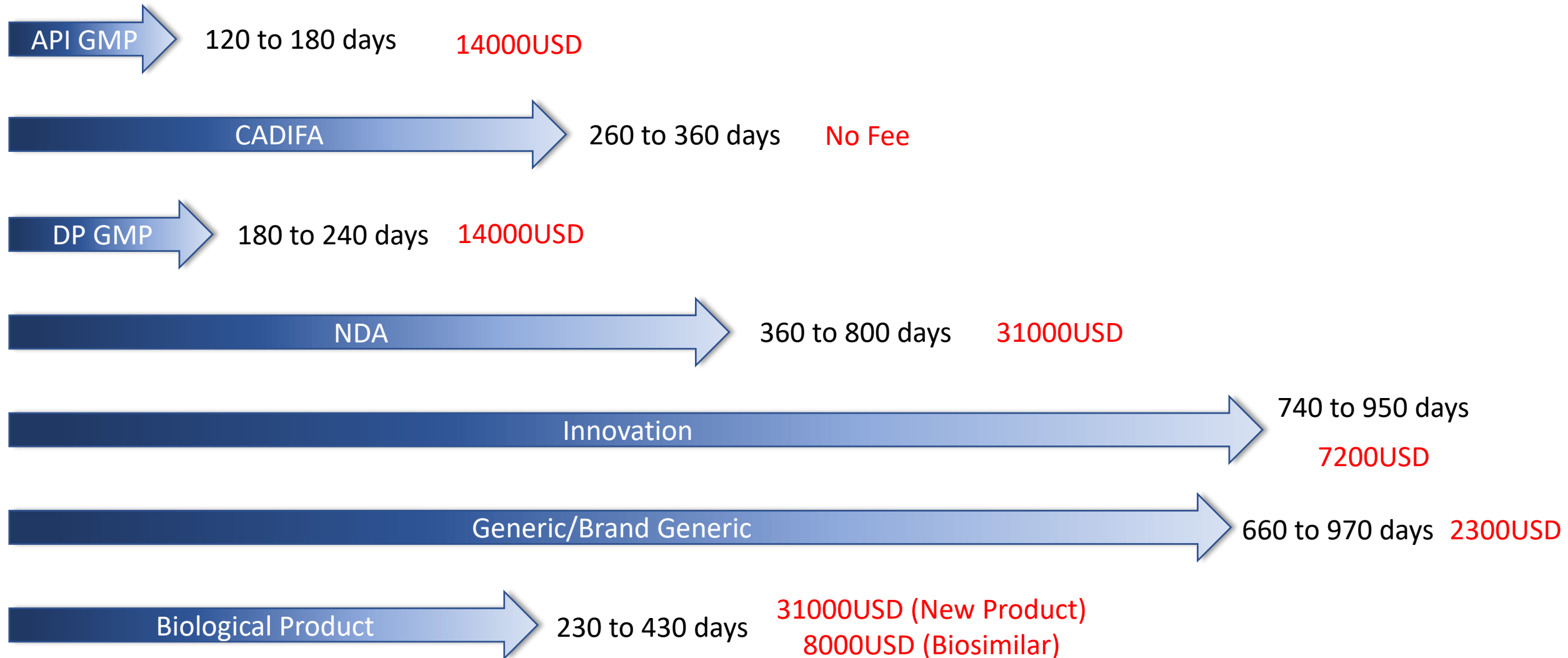
- Anvisa GMP Certification for API and Finished product
- Complete CTD format (M2, M3, M4 and M5) or Anvisa format (same information, different organization)
- M2 must be presented in Portuguese
- Accepted dossier in English or Spanish
- GMP certification required for API and Finished product

Main Requirements

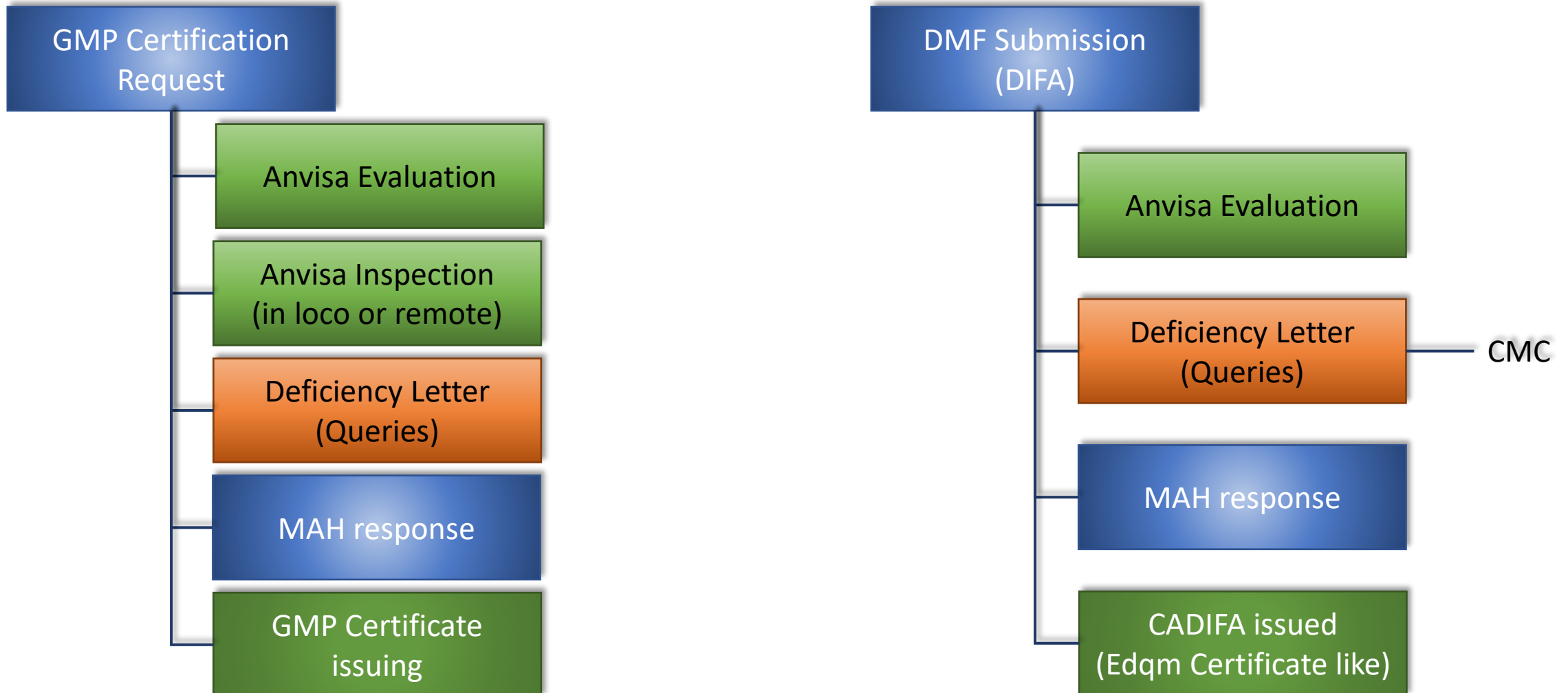
- Biosimilar Product

- Anvisa GMP certification for API and Finished product
- Complete CTD format (M2, M3, M4 and M5) or Anvisa format (same information, different organization)
- M2 must be presented in Portuguese
- Complete comparison exercise, including chemical & clinical information
- Reference drug must be the same available in Brazilian Market

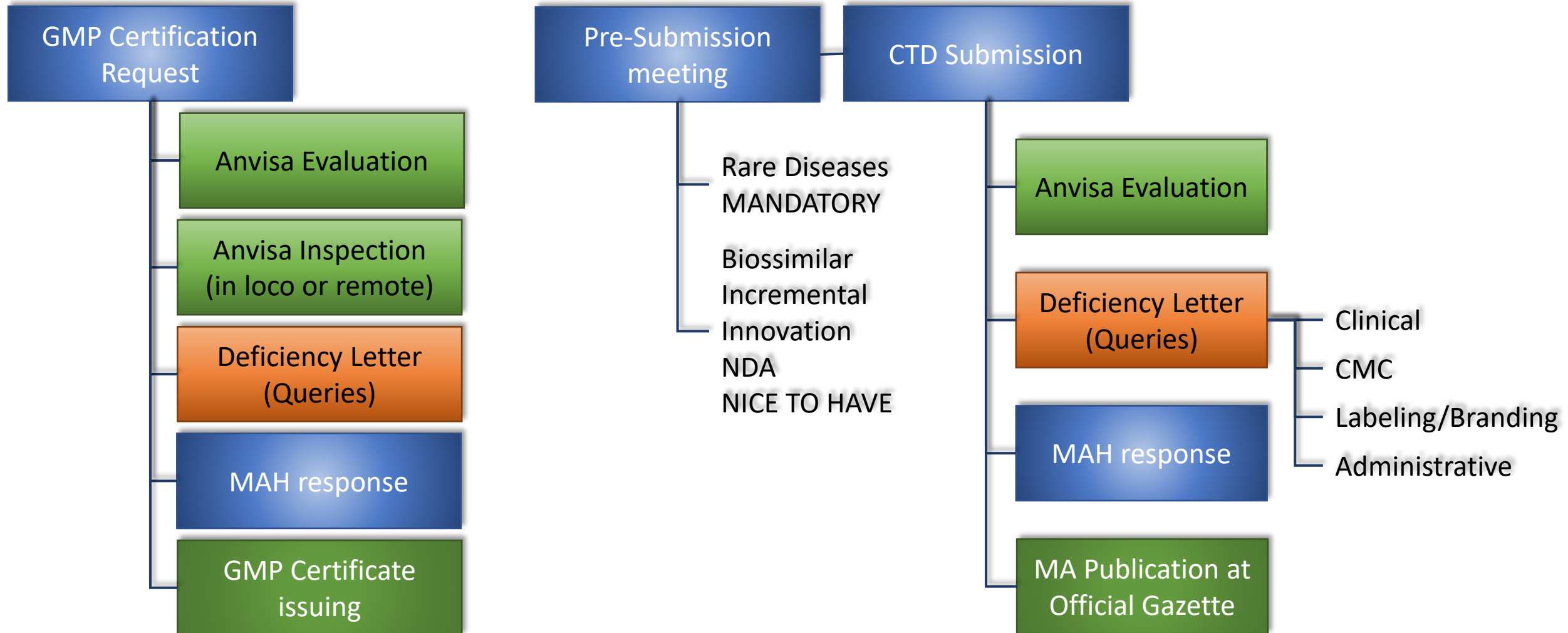
Timelines



Registration Process Flowchart - API



Registration Process Flowchart – Drug/Biological Product



Registration Process – Content and Attention Points

GMP Certification Request (API, Drug & Biological Product)

- Must be a GMP certified site by the local Authority
- Must present complete SMF and fill a local form with information about the site, lines, capabilities
- Certification issued by line (solids, semi-solids, liquids, sterile or not)
- All involved site must be certified
- Anvisa does not certify quality control and stability only sites

Registration Process – Content and Attention Points

API Notification - synthetic

- Authorization holder can be the API manufacturer, the international DP MAH or the local DP MAH
- Authorization holder must present the complete DMF, including the close part
 - DMF = DIFA
 - Authorization letter = CADIFA
- It is possible the API manufacturer to send the close part straight to Anvisa (electronic system)
- GMP request in place for the submission
- GMP certification granted for the CADIFA issuing

Registration Process – Attention Points

CTD Submission

M1 – Local Information

- GMP request in place
- Local documents
- MAH documents
- Labeling material
- API information (CADIFA & GMP)
- BSE/TSE information

M2 – Overview & Summaries

- In Portuguese

Registration Process – Attention Points

CTD Submission

M3 – CMC

- **Method validation:** Lab transfer with complete validation to the importer
- **Stability studies:** Ambient conditions – Zone IVB (30°C/75%HR)
- **Manufacturing Process Validation:** To present a summary of validation report
- **Impurities evaluation:** According to ICH M7
- **Comparison Exercise (Biossimilar):** Reference must be the one available on Brazilian Market or the same one as the approved by Anvisa (DS and DP).

Registration Process – Attention Points

CTD Submission

M4 – Pre-clinical

- According to ICH regulation

M5 – Clinical Data

- For NDA and Biological Products, Phase I, II and III studies
- For Generic/Brand Generic: BE study
- For Biosimilar Products: Applicable Clinical Studies Report (CSR)

Registration Process – Attention Points

CTD Submission (Generic/Brand Generic)

BE studies

- Conducted in a site certified by Anvisa with the Brazilian reference drug (acquired in Brazilian Market)
- Present the CSR according with the local regulation:
 - Administration time from all subjects
 - Complete analytical registries (chromatograms, for example)
 - Complete analytical method validation
 - Raw data from all subjects
 - Statistical plan and report, according to Anvisa template
 - Table with all statical data, according to Anvisa template

• Pharmaceutical Equivalence

- Physico-chemical comparison, conducted in

Life-cycle Management

- Synthetic

- Variations classified in Major, Minor and supplementary, according to the risk
- Is not completely harmonized with the ICH but follows the same philosophy.
- Major change: require to be approved prior to the implementation
 - Affect critical manufacturing aspects
 - Affect delivery system performance
 - May imply in a new BE study
- Minor change: has limited impact on quality with low risk for the product performance
 - Documents to be presented at the annual report, or individually at the implementation
 - Immediate implementation

Life-cycle Management - Major changes

- Examples of variations with impact on BE studies:
 - Major change of excipients
 - Major inclusion/change of manufacturing place
 - Major change of manufacturing process
 - Major inclusion of batch size (more than 10-fold)

Life-cycle Management

- Biological

- This regulation is much more harmonized to the ICH
- Variations classified in Major, Moderate, Minor and without impact, according to the risk
- Major and Moderate require to be approved prior to the implementation
- Minor may be implemented immediately and communicated at the annual report

Life-cycle Management - Time for approval

- New Drugs
 - 510 to 750 days
- Generic/Brand generic
 - 600 to 860 days
- Biological product
 - 240 to 390 days

Regulations in force

- **API (Synthetic)**

- DMF notification & Life-cycle management – RDC 359/2020
- GMP Guideline – RDC 654/2020

Regulations in force

- **Good Manufacturing Practices**

- GMP Guidance – RDC 658/2022
- Complementary GMP guidelines
 - Sterile products – IN 35/2019
 - Biological Products & API – IN 127/2022
 - Radiopharmaceuticals – IN 128/2022
 - Medicinal gases – IN 129/2022
 - Herbal drug products – IN 130/2022
 - Starting and packing materials – IN 131/2022
 - Liquids, creams and ointments – IN 132/2022

Regulations in force

- **Good Manufacturing Practices**

- Complementary GMP guidelines
 - Pressurized metered dose aerosol preparations for inhalation – IN 133/2022
 - Computerized system – IN 134/2022
 - Use of ionizing radiation in the manufacture of medicinal products – IN 135/2022
 - Investigational Medicinal Product – IN 136/2022
 - Medicinal products derived from human blood or plasma – IN 137/2022
 - Qualification and Validation – IN 138/2022
 - Reference and retention samples – IN 139/2022

Regulations in force

- **NDA & Generic/Brand generic**

- Registration – RDC 200/2017
- Rare disease – RDC 205/2017
- Prioritization (Neglected disease, paediatric use, among others) – RDC 204/2017
- CTD - Guide 24/2019
- Pharmacovigilance – RDC 406/2020 & IN 63/2020
- Leaflet – 47/2009
- Labeling– RDC 71/2009
- Stability Studies – RDC 318/2019 & Guide 28/2019
- Analytical Method Validation – RDC 166/2017 & Guide 10/2017
- Life-cycle management – RDC 73/2017

Regulations in force

- **NDA & Generic/Brand generic**
 - Bioequivalence:
 - BE Guidelines: RE 1170/2006
 - BE Statistical Planning and conduction: RE 898/2003
 - Protocol & CSR: RE 894/2003
 - BE Technical Report: RE 895/2003
 - BE waiver: RDC 37/2011
 - BE site certification: RDC 620/2022 & IN 123/2022

Regulations in force

- **Biological Products**

- Registration – RDC 55/2010
- Life-cycle management – RDC 413/2020 & IN 65/2020
- Stability Studies – RDC 412/2020
- All other themes, to follow the same as NDA

Questions?

Thank you very much!



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